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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,412	07/11/2001	Shohei Koide	109.050US1	8219

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VIKSNINS HARRIS & PADYS PLLP
P.O. BOX 111098
ST. PAUL, MN 55111-1098

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,412	KOIDE, SHOHEI	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/2005 has been entered.

Status of Claims

Claims 1, 4, 7-8 and 54-63 are pending in the application and are under examination.

Claims 2-3, and 9-53 have been cancelled.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A). ***New Matter Rejection***

New claims 54-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed "neutral" or "positively charged amino acid residue" as recited in e.g., claim 54 and claim 57 with an open amino acid residues at positions 7, 9 or 23 is not supported in the as-filed specification. The original disclosure describes the single, species Asn or Lys. The species do not provide support for the now broad claimed neutral or positively charged amino acid residues. The as-filed specification defines Asn as neutral amino acids but does not disclose any other neutral amino acid other than Asn. Furthermore, claim 57, which does not identify any amino acid residue(s) at position 7, 9, or 23, would likewise read on any kind of residues at these positions. The as-filed specification recites only the amino acids Asp (7, 23) and Glu (9) at these positions.

Applicant states the new limitation are supported at page 37, lines 12-24; page 38, lines 8-13; page 71, lines 13-22 and page 76, lines 6-11 of the original specification. A review of the cited section does not provide support for now broad claimed neutral or positively charged residue. The as-filed amino acid residue does not describe, except for the single amino acid residue, Asn, any other neutral amino acid or positively charged amino acid. Furthermore, the as-filed specification at page 76 discloses that the residues at positions 7 and 23 are Asp and Glu at position 9 are highly conserved in several organisms. These specific amino acids are responsible for the unfavorable electrostatic interactions and its mutations is where the crux of the invention resides. Accordingly, the species provided in the original specification does not provide support for the now broad claimed neutral or positively charged residue, especially in the surrounding context of Fn3.

B). ***Written Description***

Claims 1, 8 and 54-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons advanced in the last Office action, 11/16/2004.

Response to Arguments

Applicant cites Enzo Biochem. V. Gen-Probe Inc. and Hybritech Inc. v. Monoclonal antibodies Inc. to support their arguments that applicant is in possession of the claimed genus.

In reply, as stated in Enzo an application is complete by disclosing sufficient detail, relevant identifying characteristics of the claimed genus. However, a written description of a ***single species is not representative of the claimed genus*** of any amino acid residues. An amino acid residues as applicant points out at page 6, third incomplete paragraph of the instant REMARKS would include modified or unusual amino acids. However, the as-filed specification does not recite for single unusual or modified amino acids, especially in the context of the surrounding residues of the fibronectin molecule that would result in a stable fibronectin.

The claim is drawn to a fibronectin III(Fn3) with mutation at residues Asp 7, 23 and Glu 9 of the wild-type Fn3. These residues as disclosed in the specification, found by applicant,

are responsible for the unfavorable electrostatic interactions resulting in an unstable Fn. However, it is not apparent to date why the carboxyl triad of FNfn10 has been identified to be involved in important interactions. Koide (Biochemistry) at page 10332. Koide further states that it is not clear why these destabilizing residues are almost completely conserved in Fn10. It is apparent from Koide's article at page 10326 that a protein stabilizing effect can also be caused by pH and/or other numerous factors or forces, inter alia, salt, spatial proximity and etc. Cota (J. Mol. Biol.) at page 721, footnote, similarly states that unless mutant studies are undertaken there is some ambiguity as to whether some residues are exchanging only through a ***global exchange mechanism*** as well as some uncertainty in the estimation of very slow exchange rates that may have a half life of many weeks in a stable protein. Cota concludes the study stating, "….that even within a structural family it is difficult to generalize the relative importance of specific interactions in a protein……" See also applicant's findings at e.g., page 76. "…….It is not clear why the destabilizing residues are almost completely conserved in Fnfn10. In contrast no other FN3 domains in human fibronectin contain this carboxyl triad. The carboxyl triad of FNfn10 may be involved in important interactions ***that have not been identified to date***……."

Applicant further discloses that stability measurements cannot be performed below pH 5 due to protein aggregation, the pH dependence of TnFn3 resembles that of FNfn10. FNfn3 does not contain the carboxylate triad at positions 7, 9 and 23 indicating that the destabilization of TNfn3 at neutral pH is caused by a different mechanism than that for FNfn10. Attention is also directed to applicant's previous REMARKS (page 16, paragraph one). Applicant states that the substitution of positively charged residues for other residues would not necessarily have a stabilizing effect on a protein. A change in charge of individual amino acid residues would have differing effects on proteins, all of which have unique conformational environments. Thus, this numerous unforeseen forces would not lead a skilled artisan to the huge scope of the claimed genus drawn to any amino acid and/or positive or neutral residues.

If an applicant chooses to rely upon general knowledge in the art to render his disclosure complete, the applicant must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288, or would reasonably be expected to check the source which applicant relies upon to complete his disclosure and would be able to locate the information with no more than reasonable intelligence. There is no explicit description in the specification as to the amino

acid or the neutral and positively charged amino acids that replace(s) the 7,9 and 23 in the fibronectin structure. Claims drawn to the use of known chemical compounds must have a corresponding written description only so specific as to lead one to that class of compounds (i.e., fibronectin). In re Herschler (CCPA 1979) 200 USPQ 711. Applicant can rely upon prior art which would enable one skilled in the art to glean therefrom the necessary information to render the specification complete (or enabling) with respect to the first paragraph of 35 USC 112 but the burden is on applicant to point out precisely where the description lies in such disclosure. In re Albrecht II (CCPA 1975) 185 USPQ 590. However, not everything which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the description requirement of 112.

Applicant further argues that the electrostatic interactions of specific residues provide a place for one of skill to modify the protein to make them more stable, once a researcher determines which residues to investigate in a molecule.

In reply, while the electrostatic interactions might be the starting place to modify a protein however, as applicant states, one has to still investigate which residue(s) in this area is stabilizing. See applicant's statement above.

Notwithstanding this investigation, one has to also determine which from the numerous and different amino acid residue(s) the ones that replaces each of the wild-type residue(s), singly or in combination to stabilize the Fn. A patent is not a hunting license; it is not a reward for search, investigation or exploration, but a compensation for its successful conclusion.

Applicant further arguments merely repeat what is generally disclosed in the specification i.e., the functional definition of the modification that results in a stable molecule. These general statements, as stated in the previous Office action, are not a specific description of the claimed genus. Thus, applicant appears not to be in possession of the huge scope of any amino acid residue replacing any of the three recited positions in any type of the Fn structure, based on the evidence(s) on the record.

[This rejection may be overcome by incorporating the limitation of claims 4 and 7 to claim 1.]

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7-8 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (WO 98/56915) or Lipovsek et al (USP 6,818,418) in view of Spector et al (Biochemistry).

Koide discloses at page 6, lines 12-26 a fibronectin (Fn3) polypeptide monobody comprising a plurality of Fn3 beta-strand domain sequences that are linked to a plurality of loop region sequences. One or more of the monobody loop region sequences of the Fn3 polypeptide vary by replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3. One or more of the loop regions of the monobody comprise amino acid residues: i) from 15 to 16 inclusive in an AB loop; ii) from 22 to 30 inclusive in a BC loop and in the other loops. Koide discloses that 17 Fn3 domains are present just in human fibronectin that provides important information on conserved residues which are often important for the stability and folding. Large variations are seen in the BC and FG loops, Example XVII, page 51. See further the Examples, specifically the Tables.

Lipovsek discloses at e.g., col. 9, line 24 up to col. 10, line 68 a human 10Fn3 sequence that can be randomized, at a minimum, at amino acids 1-9 (which includes the claim 7 and 9 positions), 44-50, 61-54, 82-94 (edges of beta sheets); 21-31 (which includes the claim 23 position), 51-56, 76-88 (CDR-like solvent-accessible loops) and other solvent-accessible loops and beta turns to evolve new or improved compound-binding proteins. The mutations change the scaffold and thereby indirectly alter loop structure(s). If this approach is taken, mutations should not saturate the sequence, but rather few mutations should be introduced. Preferably, no more than 10 amino acid changes, and, more preferably, no more than 3 amino acid changes should be introduced to the beta-sheet sequences. (Lipovsek at col. 18, lines 34-45). Koide or Lipovsek does not teach that the regions containing e.g., amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction, as claimed. However, Spector at page 872 states that several residues can be destabilizing in the overall stability of a small 41-resiude helical protein. Spector further discloses that position 8 of the helical protein makes a significant, unfavorable electrostatic contribution to the overall stability. Spector further teaches that replacement of this residue with Nle or adipic acid results in a more stable protein than the wild-type

protein. Spector teaches at page 873 and page 879 that the results of their study suggest a general strategy for increasing the stability of a protein by minimizing unfavorable surface interactions. Many proteins contain clusters of positively or negatively charged residues and the results presented therein suggest that optimization of surface electrostatic interactions are likely to be a generally applicable strategy for enhancing protein stability. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine whether the amino acids in the e.g., 1-9 or 21-31 of the Fn region of Lipovsek or Koide is involved in an unfavorable electrostatic interactions as taught by Spector. Since the interactions produces instability to the helical protein hence, one would be motivated to modify these wild-type residues. The modification of these residues by any amino acid (i.e., a library, which is a collection of amino acids) is taught by e.g., Lipovsek.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the

organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
October 26, 2005